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Molecular Based Mechanisms of Mendelian Forms of Salt-Dependent Hypertension: Questioning the Prevailing Theory

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Introduction

While the molecular genetic basis of over 3000 Mendelian disorders has been determined, much less progress has been made in understanding the mechanisms through which the underlying genetic variants initiate Mendelian disease phenotypes. However, in Mendelian forms of salt-dependent hypertension in humans, it is widely believed that genetic research has successfully led to identification of the primary pathophysiologic mechanism by which genetic variants enable salt (NaCl) to initiate the increased blood pressure which characterizes these disorders. The primary mechanistic abnormality that enables initiation of the salt-induced hypertension in these Mendelian disorders is of considerable interest irrespective of whatever mechanisms may serve to sustain or exacerbate the hypertension.

Causal mutations imparting large effects on blood pressure have been reliably identified in more than a half dozen Mendelian disorders associated with salt (NaCl)-dependent hypertension (Table 1).[1-4] Prevailing theory holds that identification of these molecular genetic defects has clarified the abnormal physiologic mechanism that mediates initiation of such Mendelian forms of salt-dependent hypertension.[2, 3] Specifically, based on the coupling of results of the molecular genetic studies with the results of classic physiologic studies by Guyton and others,[5, 6] it is said that "a final common pathway" exists which mediates the initiation of all Mendelian forms of salt-dependent hypertension.[2, 3]

In this critical review, we examine the scientific evidence that is counter to the prevailing theory of "a final common pathway" proposed to account for initiation of all known Mendelian forms of salt (NaCl)-dependent hypertension in humans.[2, 3] One of the key questions we raise and that has not been considered in previous reviews of Mendelian forms of salt-dependent hypertension is: How did this theory on the initiation of all Mendelian forms of salt-dependent hypertension come to prevail even though the hemodynamic mechanism described in the theory's "final common pathway" has not been shown to mediate initiation of Mendelian forms of salt-dependent hypertension in humans or in animals? In addition to questioning whether the prevailing theory's "final common pathway" accounts for the initiation of all Mendelian forms of salt-dependent hypertension, we present a different pathway through which the genetic alterations may often mediate initiation of hypertension in these disorders.

The Prevailing Theory on How Mendelian Gene Defects Enable Salt To Initiate Hypertension

The prevailing theory holds that in all known Mendelian forms of salt-dependent hypertension in humans (Table 1), a genetically determined increase in activity of the epithelial sodium channel (ENaC) in the aldosterone sensitive distal nephron and or the sodium-chloride cotransporter (NCC) in the distal convoluted tubule is the primary mechanistic abnormality that enables salt to initiate the hypertension.[2, 3, 7, 8] If so, how do genetically induced increases in renal tubular activity of ENaC or NCC enable increases in salt intake to initiate hypertension? According to prevailing theory,

mutations that increase renal tubular activity of ENaC or NCC cause abnormally large increases in renal reabsorption of salt that increase salt balance.[2, 3, 7, 8] It is said that "mutations that increase salt balance raise blood pressure" through mechanisms that "can be readily explained via an initial increase in plasma volume and cardiac output."[7] Specifically, an abnormal increase in renal tubular activity of ENaC or NCC is held to induce an abnormally large increase in the renal reabsorption of salt and water which in turn causes abnormally large increases in intravascular volume and cardiac output and therefore blood pressure.[2, 3, 7] The level of systemic vascular resistance is said to be "normal" during the initiation of hypertension induced by increased renal reabsorption of salt.[2] This sequence of events is depicted in Figure 1 and according to Lifton et al, constitutes a "final common pathway for the pathogenesis of hypertension" including all Mendelian forms of salt-dependent hypertension.[2]

Lifton et al. have noted that according to Ohm's law, arterial pressure is proportional to two factors: cardiac output and vascular resistance.[2] As shown in Figure 1, the prevailing theory holds that an increase in renal salt reabsorption that expands plasma volume and transiently increases cardiac output is sufficient to account for the initiation of salt-dependent hypertension (Figure 1). Since systemic vascular resistance is said to remain “normal” during the initiation of salt-induced increases in blood pressure, the theory holds that abnormalities in systemic vascular resistance are not involved in the initiation of salt-induced hypertension. The theory holds that vascular resistance becomes abnormal only later through a phenomenon termed

"autoregulation" which reverses cardiac output towards normal and gives rise to the increased systemic vascular resistance that enables the hypertension to persist.[2, 9-12]

Questioning the Prevailing Theory

The prevailing theory of the pathogenesis of Mendelian forms of salt-dependent hypertension is said to "fit nicely into our understanding of the physiology of blood pressure regulation, with the increased intravascular volume resulting in increased cardiac output due to increased stroke volume and a rise in blood pressure according to Ohm's law."[13] This theory, which could also be termed the "volume-loading/cardiac output" theory, rests on the untested assumption that genetic variants that increase renal tubular activity of ENaC or NCC hemodynamically account for the *initiation* of all Mendelian forms of salt-dependent hypertension entirely by transiently causing abnormally high levels of cardiac output, , i.e., without also usually causing, or needing to be accompanied by, an abnormality in systemic vascular resistance (Figure 1). Accordingly, the current analysis focuses on several related questions: 1) Is, or is not, the hemodynamic initiation of all known Mendelian forms of salt-dependent hypertension in humans (Table 1) usually mediated through a transient, abnormally high level of cardiac output and a normal level of systemic vascular resistance? 2) In individuals with mutations underlying Mendelian forms of salt-dependent hypertension (Table 1), and who consume typical modern diets with abundant amounts of salt, are mutation-dependent increases in renal tubular activity of ENaC or NCC usually sufficient to account for induction of the hypertension ? Or must the mutations also do something

else ? 3) In individuals with these mutations who consume abundant amounts of salt, are mutation-dependent increases in renal tubular activity of ENaC or NCC even necessary to account for increased risk of salt-dependent hypertension? Or could the mutations increase risk for salt-dependent hypertension even if they did not cause increases in renal tubular activity of ENaC or NCC ?

The Prevailing Theory on How Mendelian Gene Defects Enable Salt to Initiate Hypertension: What is the Hemodynamic Evidence ?

What is the evidence for the prevailing theory that an abnormally high level of cardiac output, but not of systemic vascular resistance, mediates the hemodynamic initiation of Mendelian forms of salt-dependent hypertension (Figure 1)?[2] Surprisingly, there are no published studies of the serial changes in cardiac output and systemic vascular resistance that occur in humans or in animals during initiation of salt-induced hypertension in these disorders. This raises the question: On what hemodynamic evidence is the theory based?

Some Mendelian forms of salt-dependent hypertension are characterized by increased circulating levels of mineralocorticoid hormones such as aldosterone or deoxycorticosterone (Table 1). Therefore, in support of the prevailing theory, some investigators[3] have cited studies by Montani, Guyton, and others of the hemodynamic changes, i.e., changes in cardiac output and systemic vascular resistance, that occur during initiation of salt retention and hypertension induced by administering

aldosterone to animals ingesting a high salt diet.[6] However, as discussed further below, the cited studies of Montani et al[6] do not include adequate controls. When the results of studies using appropriate normal controls are taken into consideration, it becomes apparent that the prevailing theory does not adequately explain how the combination of excess aldosterone and a high salt diet initiates hypertension.

Is An Aldosterone-Dependent Abnormality in Systemic Vascular Resistance Involved in the Initiation of Hypertension Induced by Aldosterone and a High Salt Diet ?

As shown in Fig. 2a,b,c, hemodynamic studies by Montani et al demonstrate that systemic vascular resistance appears to begin increasing above baseline during the initiation of salt retention and increased blood pressure induced by intravenous administration of large amounts of aldosterone to dogs ingesting a high salt diet (approximately 6 mmol/kg body weight/day).[6] This raises the question: When salt retention is induced by aldosterone and a high salt diet, is an aldosterone-dependent abnormality in systemic vascular resistance involved in initiation of the hypertension? To address this question, one must first define what constitutes a normal level of vascular resistance in response to initiation of salt retention with a high salt diet alone, i.e., without supplemental aldosterone. Unfortunately, Montani et al did not report the *changes* in systemic vascular resistance that normally occur in control dogs when salt-retention is induced by increasing salt intake alone, i.e., without supplemental aldosterone (Fig. 2a,b,c).[6] However, other investigators have reported the changes in

systemic vascular resistance that occur in normal control dogs when salt retention is induced by administering a high salt diet without supplemental aldosterone.[14]

In normal salt-resistant control dogs maintained on a low salt diet and not given aldosterone, studies by Krieger et al demonstrate that the normal cardiovascular response during the onset of sodium retention induced by greatly increasing salt intake alone (from < 0.5 mmol/kg/day to 7 mmol/kg/day), is a near 10% increase in cardiac output (Fig. 2d) together with vasodilation and a near 10% decrease in systemic vascular resistance (Fig. 2e).[14] Thus, in normal control dogs not given aldosterone, the distinct increase in cardiac output observed during the onset of sodium retention induced by greatly increasing salt intake alone is not sufficient to increase blood pressure because the normal animals, i.e., animals not given aldosterone, vasodilate and decrease systemic vascular resistance (Fig. 2d,e,f). Studies by DeClue et al have shown that normal control dogs not treated with aldosterone can tolerate massive salt loading (up to 20 - 34 mmol/kg/day) and massive sodium retention (as judged by increases in ^{22}Na space) without developing hypertension.[15] In contrast, the presumed sodium retention and the increases in cardiac output that occur upon administration of aldosterone to dogs ingesting a high salt diet (~ 6 mmol/kg body weight/day), are associated with the onset of hypertension because the increases in cardiac output are not accompanied by normally expected, pressor offsetting decreases in systemic vascular resistance (Fig 2a,b,c). [6]

In light of the observations of Krieger et al (Fig. 2,d,e,f)[14] and DeClue et al[15] made during induction of salt retention in normal control dogs not given aldosterone, the studies of Montani et al (Fig. 2a,b,c)[6] indicate that during induction of salt retention by administration of aldosterone with a high salt diet, an aldosterone-dependent failure to normally reduce systemic vascular resistance is involved in initiation of hypertension. This aldosterone-dependent failure to normally vasodilate and rapidly reduce systemic vascular resistance during the onset of salt retention is not apparent from the studies of Montani et al because their experiments did not include the requisite normal control group, i.e., did not include a separate control group of normal salt-resistant dogs studied before and during salt retention induced by administering a very high salt diet alone, i.e., without supplemental aldosterone.[6] Nor did they include any experiments measuring the effects on cardiac output and vascular resistance of initiating aldosterone treatment in animals ingesting control diets containing low amounts of salt. The foregoing observations are at odds with the prevailing theory that an abnormality in systemic vascular resistance is not involved in the initiation of hypertension in patients with Mendelian disorders characterized by abnormally high levels of aldosterone. These observations are consistent with the possibility that an aldosterone-dependent abnormality in systemic vascular resistance, i.e., an aldosterone-dependent failure to normally vasodilate and reduce systemic vascular resistance during salt retention, is involved in the initiation of salt-dependent hypertension in Mendelian disorders characterized by abnormally high levels of aldosterone (Table 1).

How Does the Combination of Deoxycorticosterone and a HIgh Salt Intake Initiate Hypertension ? Implications for the Pathogenesis of Mendelian Forms of Hypertension With Increased Circulating Levels of Deoxycorticosterone

Disorders of congenital adrenal hyperplasia (CAH) that are caused by mutations that decrease activity of 11β-hydroxylase or 17α-hydroxylase are often associated with hypertension.[1] These disorders were the first Mendelian forms of hypertension in which the responsible genes were cloned and causative mutations identified, originally through the work on 11β-hydroxylase deficiency by White et al,[1, 16] and on 17α-hydroxylase deficiency by Waterman's laboratory[17, 18] Decreases in activity of either of these enzymes can give rise to increased circulating levels of mineralocorticoid hormones including deoxycorticosterone (DOC). There are no published studies of the serial changes in cardiac output and systemic vascular resistance that occur during initiation of salt-dependent increases in blood pressure in humans or animals with mutations in 11β-hydroxylase or 17α-hydroxylase. However, there are published studies of the systemic hemodynamic changes that occur during initiation of salt-dependent increases in blood pressure in animals given DOC or metyrapone, a pharmacologic inhibitor of 11β-hydroxylase.

Obst et al reported that in mice, increases in systemic vascular resistance, not increases in cardiac output, mediate the initiation of hypertension induced by administration of deoxycorticosterone and salt (DOC-NaCl).[19] The finding that DOC-NaCl treatment can induce hypertension even when increases in cardiac output are

prevented by beta-adrenergic blockade also indicates that increases in cardiac output are not always necessary for DOC-NaCl to initiate hypertension.[20] Similarly, Miller and colleagues reported that in some pigs, administration of deoxycortisterone together with ~ 5 mmol NaCl/kg body weight/day initiated hypertension by inducing increases in systemic vascular resistance without inducing increases in cardiac output.[21] In other pigs, the hypertension was initiated by increases in cardiac output that were not offset by decreases in systemic vascular resistance that might normally be expected to occur with salt retention.[21] In studies by Ferrario et al in dogs given deoxycorticosterone together with ~ 5 mmol NaCl/kg body weight/day, blood pressure increased with salt retention because systemic vascular resistance failed to sufficiently decrease and offset the pressor effect of a 20% increase in cardiac output.[22] Thus, Ferrario et al concluded that "alterations in vascular reactivity may play a role in the elevated pressure associated with DOC excess".[22] Unfortunately, none of these studies of DOC-NaCl hypertension included a control group of normal salt-resistant animals studied before and during salt retention induced by administering a high salt diet alone, i.e., without DOC. Nevertheless, the results of all of these hemodynamic studies performed during induction of salt retention by administering DOC and NaCl, are consistent with the possibility that a mineralocorticoid-dependent abnormality in systemic vascular resistance, i.e., a failure to normally decrease systemic vascular resistance during salt retention, is often required for the combination of DOC and NaCl to initiate hypertension.

The Mendelian form of salt-dependent hypertension caused by mutations that impair 11β-hydroxylase activity [1, 2] can be pharmacologically mimicked by giving salt and metyrapone, an inhibitor of 11β-hydroxylase. To investigate the mechanisms whereby inhibition of 11β-hydroxylase enables salt to induce hypertension in dogs, Bravo et al studied the hemodynamic effects induced by administering metyrapone with a low salt diet or with a high salt diet.[23] They found that in dogs given a low salt diet, metyrapone caused a 31% increase in cardiac output and a simultaneous decrease in total peripheral resistance such that blood pressure did not change.[23] However, initiation of a high salt diet in these metyrapone treated dogs induced a "prompt" increase in blood pressure by causing an increase in total peripheral resistance without causing a further increase in cardiac output.[23] Therefore, Bravo et al concluded that increases in cardiac output do not provide a sufficient explanation for how inhibition of 11β-hydroxylase activity enables salt to initiate hypertension.[23] These observations are at odds with the prevailing theory for initiation of Mendelian forms of salt-dependent hypertension which are characterized by increased circulating levels of mineralocorticoids such as DOC and DOC metabolites.[2]

How Does Salt Initiate the Increased Blood Pressure in Mendelian Forms of Salt-Dependent Hypertension That Do Not Involve Increased Circulating Levels of Mineralocorticoids ?

At least 4 Mendelian forms of salt-dependent hypertension have been described in which the increased blood pressure does not appear to involve increased circulating

levels of mineralocorticoids (Table 1). There are no published studies of the changes in cardiac output and systemic vascular resistance that occur during initiation of salt-induced increases in blood pressure in humans or animals with any of the gene defects underlying these Mendelian forms of salt-dependent hypertension. This raises the question, what is the hemodynamic evidence for the prevailing theory (Figure 1) for initiation of salt-induced hypertension in these Mendelian disorders? In support of the theory, some investigators[7, 13] have cited the work of Guyton and colleagues.[5, 10, 12]

Guyton et al studied the serial hemodynamic changes that occur during initiation of a non-genetic form of salt-dependent hypertension induced by administering large amounts of salt to dogs in which renal mass had been surgically reduced by 70%.[5, 10, 12] In this model in which aldosterone levels do not appear to be increased,[24] Guyton et al concluded that salt loading induces hypertension by causing transient, abnormally large increases in cardiac output while systemic vascular resistance initially remains normal, i.e., unchanged.[12, 25-27] However, those studies of Guyton and colleagues did not include measurements of the changes in cardiac output and systemic vascular resistance that occur during initiation of salt loading in normal salt-resistant control dogs with intact kidneys. Because the studies of Guyton et al lacked such measurements in normal controls, it is not possible to determine whether the responses they observed in cardiac output or systemic vascular resistance during initiation of salt loading and hypertension were normal or abnormal.

In studies in normotensive salt-sensitive humans and animals that have included salt-resistant normal controls, an abnormal systemic vascular resistance response to salt loading, not a transient abnormal cardiac output response to salt loading, is the salt-dependent hemodynamic abnormality that usually mediates *initiation* of the salt-induced increases in blood pressure.[28-33] Specifically, throughout initiation of salt loading in most salt-sensitive normotensive subjects tested, the increases in sodium balance and transient increases in cardiac output are not abnormally high, i.e., not greater than those occurring during salt-loading in salt-resistant normal controls.[29,30,33] Salt loading usually induces substantial and readily detectable increases in salt retention and transient increases in cardiac output in salt-resistant normotensive controls as well as in salt-sensitive normotensive subjects.[29,30,33] In contrast, throughout initiation of salt loading in most salt-sensitive normotensive subjects, systemic vascular resistance is abnormal because it fails to decrease to a normal extent, i.e., to the same extent as that usually observed during salt loading in salt-resistant normal controls.[29,30,33] Thus, the prevailing theory's "final common pathway" for initiation of salt-dependent hypertension is inconsistent with the results of salt-loading studies in salt-sensitive normotensive subjects versus salt-resistant normotensive controls.

The Importance of Salt Loading Studies in Normotensive Subjects

We are focusing on the results of salt loading studies in normotensive subjects rather than on those in hypertensive subjects because we are mainly interested in the

mechanisms whereby dietary salt *initiates* hypertension rather than the mechanisms whereby dietary salt exacerbates hypertension. The mechanisms whereby salt exacerbates hypertension may not reflect the mechanisms whereby salt initiates hypertension and could be influenced by the duration of pre-existing hypertension and other confounding factors which are difficult to ascertain. It should be noted that the results of hemodynamic and metabolic studies of dietary salt loading that compared salt-sensitive hypertensives versus salt-resistant hypertensives[34, 35] differ from the results of those that compared salt-sensitive normotensives versus salt-resistant normotensives.[28-30, 35] It is also important to note that the salt loading study comparing salt-sensitive hypertensives versus salt-resistant hypertensives[34] did not include normal controls, i.e., normotensive, salt-resistant individuals. Because that study did not include normal controls, it did not determine whether the cardiac output and sodium balance responses to salt loading were normal or abnormal in the salt-sensitive hypertensives or in the salt-resistant hypertensives.

The normal response to initiation of salt loading, i.e., the usual response in salt-resistant, normotensive controls, is a rapid and substantial decrease in systemic vascular resistance.[29,30,33] Accordingly, in salt-sensitive normotensive subjects, the observation that systemic vascular resistance usually changes little from baseline during initiation of salt-induced increases in blood pressure, signals the existence of an abnormality in systemic vascular resistance that often plays a critical role in the initiation of salt-induced hypertension. The prevailing, "volume-loading/cardiac output" theory for the pathogenesis of Mendelian forms of salt-dependent hypertension does not take

into account the fact that the normal response to initiation of salt loading is vasodilation and a decrease in systemic vascular resistance.[28-33] Thus, the prevailing theory overlooks the possibility that mutations causing Mendelian forms of salt-dependent hypertension enable salt to initiate the hypertension by causing an abnormality in systemic vascular resistance, specifically, a failure to normally vasodilate and decrease systemic vascular resistance in response to salt loading.

A "Vasodysfunction" Theory To Explain How Mendelian Gene Defects Enable Salt To Initiate Hypertension

We propose that for molecular genetic alterations to enable salt to initiate Mendelian forms hypertension, they must often cause "vasodysfunction", i.e., a failure to normally vasodilate and decrease systemic vascular resistance in response to salt loading (increases in salt intake) (Figure 3). In contrast to the prevailing, "volume-loading/cardiac output" theory which holds that systemic vascular resistance is normal during the initiation of salt-induced hypertension (Figure 1), the "vasodysfunction" theory holds that a mutation-dependent abnormality in vascular resistance, i.e., the failure to normally vasodilate in response to salt loading, often mediates the ability of salt to initiate the hypertension in Mendelian disorders of hypertension. While the current analysis is focused on the hemodynamic events that *initiate* the salt-dependent increase in blood pressure, Figure 3 also depicts the changes in cardiac output and systemic vascular resistance believed to occur after the blood pressure has increased. The "vasodysfunction" theory leaves open the possibility that the mutations in these

disorders may not only mediate the failure to normally vasodilate during initiation of the salt-induced increases in blood pressure, they might also contribute to the abnormal increases in vascular resistance that occur after the BP has initially increased and that sustain the salt-dependent hypertension. Unlike the prevailing, "volume-loading/cardiac output" theory, the "vasodysfunction" theory accommodates the results from properly controlled studies demonstrating that a failure to normally vasodilate and decrease systemic vascular resistance in response to salt-loading, is often involved in the initiation of salt-induced increases in blood pressure in normotensive, salt-sensitive animal models and in normotensive, salt-sensitive humans.[28-33]

Systemic vascular resistance (also known as total peripheral resistance) is conventionally defined as the overall resistance of the entire resistance vasculature and according to the "vasodysfunction" theory, the inability to normally decrease systemic vascular resistance in response to salt includes an inability to normally decrease renal vascular resistance in response to salt (see legend to Figure 3 for a discussion of the role of abnormal renal vascular resistance in initiating and sustaining salt-induced hypertension). If the mutations were not associated with salt-induced "vasodysfunction," even large increases in salt intake and salt retention would not necessarily initiate hypertension because the pressor effects of salt-induced increases in cardiac output would be offset by countervailing depressor effects of normal salt-induced decreases in systemic vascular resistance.

Most normal salt-resistant humans can tolerate large increases in salt intake and salt retention without developing substantial increases in blood pressure because they vasodilate and decrease systemic vascular resistance in response to salt loading.[29, 30, 36] While extreme increases in salt intake, i.e., increases to levels more than 2 - 3 fold greater than the upper limit of salt intake of most people in modern societies, may induce increases in blood pressure in most normal individuals[36], non-extreme increases in salt intake to levels within the usual range of salt intake observed in modern societies do not [29, 30, 36, 37]. It should also be noted that in normotensive humans studied under tightly controlled dietary and environmental conditions for up to 200 days during which salt intake was varied between 6 grams/day to 12 grams/day, blood pressure showed no correlation with variations in sodium balance.[38]

It is conceivable that under some unusual circumstances, e.g., when someone with a rare genetic defect that severely limits sodium excretory capacity increases their salt intake to an unusually high level (i.e., to a level well beyond the average amount of salt consumed in most populations), the increases in sodium retention and cardiac output might become sufficient to initiate hypertension. That is, the increases in salt retention and cardiac output might become so great that they induce increases blood pressure even if the vasodilatory responses to salt retention are as large as normally possible. However, according to the proposed vasodysfunction theory (Figure 3), this is not the usual mechanism whereby the genetic alterations underlying Mendelian forms of hypertension enable increases in salt intake within usual dietary ranges to initiate the hypertension.

How Could the Gene Defects Underlying Most Mendelian Forms of Salt-Dependent Hypertension Cause Subnormal Vasodilatory Responses to Salt ?

Here we briefly discuss some of the mechanisms whereby mutations in Mendelian disorders of salt-dependent hypertension could potentially impair the normal ability to decrease systemic vascular resistance in response to increases in salt intake. The gene defects underlying at least 6 of the 7 known Mendelian forms of salt-dependent hypertension all appear to promote increased activity of epithelial sodium channels. It is well recognized that epithelial sodium channels or epithelial like sodium channels may be expressed not just in the renal tubule, but also in other tissues including the brain and the vasculature.[39-42] There is mounting evidence that alterations in activity of such epithelial sodium channels in the brain and vasculature can influence blood vessel function in ways that could influence vascular resistance and impair normal vasodilatory responses to changes in salt intake. For example, the work of Leenen's group has indicated that in Liddle syndrome, increases in ENaC activity in the brain may be necessary for initiation of salt-induced hypertension, perhaps by promoting increases in sympathetic outflow in response to salt-induced changes in cerebrospinal fluid sodium concentration, i.e., by promoting increases in neural activity that could interfere with normal vasodilatory responses to increases in salt intake.[43] Jeggle et al have shown that mutations causing Liddle syndrome may also increase ENaC activity and cortical membrane stiffness in vascular endothelial cells before the onset of salt-induced hypertension.[44] The studies of Perez et al indicate that increases in ENaC

activity in the endothelium can negatively modulate nitric oxide activity in resistance arteries, and they have also shown that blocking ENaC can enhance flow mediated vasodilation.[45] Thus, in concert with increases in cardiac output that can normally occur with salt loading, increases in ENaC activity in the brain and or vasculature could mediate initiation of salt-induced hypertension by impairing the ability of blood vessels to normally dilate and reduce vascular resistance in response to salt loading.

The prevailing theory on how salt initiates Mendelian forms of hypertension[2, 3] does not take into account the evidence that epithelial sodium channels are expressed in many cell types besides just the renal tubular epithelium.[39-42] The theory[2, 3] also does not take into account the possibility that during the initiation of Mendelian forms of salt-dependent hypertension characterized by increases in mineralocorticoid levels, the mineralocorticoids could be impairing normal vasodilatory responses to salt by affecting the activity of a variety of ion channels in the vasculature in addition to ENaC. It is now well recognized that mineralocorticoids and mineralocorticoid receptors have effects on several ion channels outside the renal tubule that can affect vascular function in ways that could contribute to the initiation of salt-dependent hypertension.[46] It is also conceivable that is some Mendelian disorders, the mutations disturb the distribution of salt in tissues such as the brain and or vasculature and this in turn affects vascular function in a manner that impairs the ability to normally vasodilate in response to salt.

Familial hyperkalemic hypertension (FHHt) is a group of Mendelian disorders in which the prevailing theory holds that the causative mutations enable salt to initiate

hypertension by causing abnormally high levels of salt retention and cardiac output secondary to increases in activity of the Na-Cl cotransporter (NCC) in the distal convoluted tubule.[3, 7, 8] However, there are no published studies showing that FHHt mutants enable salt to initiate hypertension entirely by enabling a given salt load to induce greater levels of *both* salt retention and cardiac output than those induced by the same salt load in wild type controls. The studies showing that NCC knockout causes low blood pressure in animals harboring an FHHt mutant do not establish that increases in NCC activity are required for FHHt mutants to enable salt to initiate hypertension.[8] The prevailing theory depends on the assumption that because the various FHHt mutations have been found to cause increases in NCC activity that are associated with the ability of salt loading to induce hypertension, the mutation-induced increases in NCC activity are necessary and sufficient for salt loading to initiate the hypertension. This view presupposes that the mutations are not capable of causing effects on vascular resistance that are necessary or sufficient to enable salt loading to initiate the hypertension. All of the genes that cause FHHt encode proteins that are expressed not just in the renal tubule, but also outside the renal tubule where they could conceivably act to affect vascular function and the ability of salt to modulate vessel tone and initiate hypertension. Unlike the vasodysfunction theory (Figure 3), the prevailing theory on how FHHt mutants enable salt to initiate hypertension does not take into account the growing body of evidence indicating potential effects of FHHt mutations on the function of proteins that regulate vascular resistance.[47-50]

Are Genetically Induced Increases in Net Salt Retention and Cardiac Output Necessary for Mendelian Gene Defects to Enable Salt Loading to Initiate Hypertension ?

In addition to holding that an abnormality in vascular resistance is often required for Mendelian gene defects to enable salt to initiate the hypertension, the "vasodysfunction" theory (Figure 3) raises a related issue: For the gene defects to enable an increase in salt intake to initiate hypertension, is it necessary for the mutations to induce greater increases in net salt retention and cardiac output than would otherwise be induced by an increase in salt intake in the absence of the mutations? In humans and in animal models with mutations that underlie the Mendelian forms of salt-dependent hypertension shown in Table 1, it has not been demonstrated that *mutation-dependent* increases in renal salt retention and cardiac output are necessary for the mutations to enable increases in salt intake to initiate the hypertension. That is, it has not been shown that mutation-induced increments in net salt retention and cardiac output beyond those induced by increasing salt intake in wild type, normal salt-resistant subjects, are necessary for the mutations to enable an increase in salt intake to initiate hypertension. Accordingly, the vasodysfunction theory (Figure 3) leaves open the possibility that mutation-dependent increases in renal tubular epithelial sodium transport which cause increases in salt retention and cardiac output, may not always be necessary for the mutations to enable increases in salt intake to initiate the hypertension.

The foregoing considerations raise specific questions about the prevailing theory for the pathogenesis of various Mendelian forms of salt-dependent hypertension, questions that have yet to be experimentally addressed. For example, are increases in renal salt retention caused by Liddle syndrome mutations in ENaC within the renal tubule even necessary for the initiation of salt-induced hypertension observed in Liddle syndrome ? Or could selective expression of a Liddle ENaC mutation in all its usual sites of expression except in the renal tubule enable increased salt intake to initiate and sustain the increased blood pressure, i.e., could such selective expression of a Liddle ENaC mutation convert wild type, normotensive salt-resistant control animals into salt-sensitive animals ? It remains to be established whether increases in salt retention caused by Liddle syndrome mutations in ENaC within the renal tubule are necessary for the initiation of salt-induced hypertension in Liddle syndrome. It has been reported that in a mouse model of Liddle syndrome, general knockout of the ubiquitin ligase Nedd4-2 increased tissue levels of all ENaC subunits and enabled dietary salt loading to initiate hypertension, yet the mutation did not reduce the amount of sodium excreted in the urine; throughout salt loading, the amount of sodium excreted by mutant animals was the same as that excreted by wild type, salt-resistant controls.[51] The wild type, salt-resistant controls tolerated the large salt load without developing increased blood pressure despite retaining apparently large amounts of sodium.

The Level of Salt Retention is Not a Reliable Surrogate for the Level of Cardiac Output

It should be noted that even if one happens to observe reduced urinary excretion of sodium and an abnormally high level of salt retention during initiation of salt loading and hypertension in a Mendelian disorder of increased blood pressure, such observations cannot be considered reliable surrogate evidence for the presence of abnormally high levels of central blood volume and cardiac output, i.e., levels of central blood volume and cardiac output greater than those achieved during salt loading in normal salt-resistant controls. Recent studies by Titze et al have shown that large amounts of sodium can be retained without retention of commensurate amounts of water.[52, 53] Thus, it cannot be reliably assumed that increases in sodium retention will always be accompanied by commensurate increases in central blood volume and cardiac output. There are no reports showing that during the initiation of salt loading in humans or animals with mutations causing Liddle syndrome, or any other Mendelian form of salt-dependent hypertension, that sodium balance and cardiac output are *both* greater than in salt-loaded wild type normal controls. Interestingly, in an animal model of apparent mineralocorticoid excess and dysregulation of ENaC activity induced by genetic deficiency of 11β- hydroxysteroid dehydrogenase type 2 (11βHSD2), the initiation of salt loading was associated with greater sodium retention and blood pressure but lower plasma volume than in salt-loaded wild type controls.[54] According to Bailey et al, this observation "challenges the assumption that the salt-sensitive phenotype is an uncomplicated renal phenomenon."[54]

Summary and Conclusion

This critical review directly challenges the prevailing theory that a transient increase in cardiac output caused by genetically mediated increases in activity of the epithelial sodium channel (ENaC) in the aldosterone sensitive distal nephron, or of the sodium-chloride cotransporter (NCC) in the distal convoluted tubule, accounts entirely for the hemodynamic initiation of all Mendelian forms of salt-dependent hypertension (Figure 1).[2, 3, 7, 8] The prevailing theory of how genetic mutations enable salt to hemodynamically initiate Mendelian forms of salt-dependent hypertension in humans (Figure 1)[2] depends on the results of salt-loading studies of cardiac output and systemic vascular resistance in non-genetic models of hypertension that lack appropriate normal controls. The theory is inconsistent with the results of studies that include measurements of the initial hemodynamic changes induced by salt loading in normal, salt-resistant controls. The current analysis, which takes into account the results of salt-loading studies that include the requisite normal controls, indicates that mutation-induced increases in the renal tubular activity of ENaC or NCC that lead to transient increases in cardiac output will generally not be sufficient to enable increases in salt intake to initiate the increased blood pressure that characterizes Mendelian forms of salt-dependent hypertension (Table 1). The current analysis also raises questions about whether mutation-dependent increases in renal tubular activity of ENaC or NCC are even necessary to account for increased risk for salt-dependent hypertension in most patients with such mutations.

We propose that for the genetic alterations underlying Mendelian forms of salt-dependent hypertension to enable increases in salt intake to initiate the increased blood pressure, they must often cause "vasodysfunction", i.e., an inability to normally vasodilate and decrease systemic vascular resistance in response to increases in salt intake within dietary ranges typically observed in most modern societies. A subnormal ability to vasodilate in response to salt loading could be caused by mutation related disturbances originating in the vasculature itself or in sites outside the vasculature (e.g., brain or adrenal glands) that have the capacity to affect vascular function.

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Figure Legends

Figure 1. The prevailing theory for the pathogenesis of Mendelian forms of salt-dependent hypertension. Adapted from Lifton et al[2] with permission from Elsevier. This sequence of events has been proposed to represent "a final common pathway for the pathogenesis of hypertension."[2] According to Lifton et al, "All inherited and acquired forms of hypertension share increased net salt balance as an inciting factor. Increased intravascular volume and volume delivery to the heart augment cardiac output and therefore blood pressure."[2] In this formulation,[2] systemic vascular resistance is explicitly held to be normal during the onset of hypertension and thus, salt-induced abnormalities in systemic vascular resistance are not involved in initiation of the salt-induced hypertension. The level of systemic vascular resistance is said to become abnormal only after blood pressure has increased and only after the increased cardiac output has initiated the phenomenon of autoregulation.[2] Note that this pathway does not display, or take into consideration, the changes in cardiac output and systemic vascular resistance that occur in normal, salt-resistant controls when salt retention is induced by increasing dietary intake of salt. The term systemic vascular resistance is synonymous with the term total peripheral resistance.

Figure 2. Sequential hemodynamic changes that occur with initiation of salt retention in dogs. **(A,B,C)** Changes in cardiac output, systemic vascular resistance, and mean arterial pressure, respectively, that occur when salt retention is induced by switching dogs from a high salt intake without concomitant administration of aldosterone, to a

high salt intake with concomitant administration of aldosterone (adapted from Montani et al).[6] **(D,E,F)** Changes in cardiac output, systemic vascular resistance, and mean arterial pressure, respectively, that occur when salt retention is induced by switching normal dogs from a low salt intake to a high salt intake without giving supplemental aldosterone (adapted from Krieger et al).[14] Note that in normal control dogs (D,E, F) in which salt retention is initiated by a high salt intake alone (without supplemental aldosterone), cardiac output increases and systemic vascular resistance decreases such that blood pressure does not change. In contrast, in the experimental dogs in which salt retention is induced by the combination of a high salt intake with supplemental aldosterone (A,B,C), cardiac output increases but systemic vascular resistance fails to decrease. The different blood pressure responses between aldosterone treated dogs (C) and normal dogs (F) are largely due to different vascular resistance responses to salt retention (B versus E), not different cardiac output responses to salt retention (A versus D).

Figure 3. The "vasodysfunction" theory for the initiation of Mendelian forms of salt-dependent hypertension (Table 1). **(a)** Common pathway in normal, non-mutant subjects that yields a normal (non-pressor) response to increases in salt (NaCl) intake within the range of usual daily salt intake observed in modern societies. In normal subjects, such non-extreme yet substantial increases in salt intake often induce substantial increases in salt retention[29, 30, 35, 36, 37] and transient increases in cardiac output[29, 30] but typically do not initiate hypertension because potential pressor effects of even large salt-induced increases in cardiac output (+10%) are normally offset by

depressor effects of salt-induced decreases in systemic vascular resistance.[29, 30] Systemic vascular resistance is conventionally defined as the combined resistance of the entire resistance vasculature. Note that in this normal pathway, a decrease in renal vascular resistance in response to salt loading contributes to the decrease in systemic vascular resistance in response to salt. When salt intake is increased, the associated decrease in renal vascular resistance also facilitates renal excretion of salt (salt output), thereby contributing to the achievement of steady state salt balance (i.e., the steady state in which salt output matches salt intake). However, when salt intake is increased, salt balance is not immediately achieved in normal individuals. Because of the delay in achieving salt balance in normal humans, increases in salt intake can cause substantial increases in body salt content[29,30, 35, 36, 37] and increases in cardiac output.[29, 30] In this pathway, salt-induced decreases in renal vascular resistance are held to : 1) contribute to the salt-induced decreases in systemic vascular resistance that hemodynamically prevent salt-induced increases in cardiac output from causing hypertension, and 2) contribute to the achievement of salt balance by facilitating sodium excretion.

Note that while this pathway is focused on the initiation phase of salt-loading, it also depicts changes in cardiac output and systemic vascular resistance that transpire after the salt-induced increase in cardiac output and the salt-induced decrease in systemic vascular resistance have occurred. In salt resistant normotensive humans, it has been shown that after occurrence of the salt-induced increase in cardiac output and the salt-induced decrease in systemic vascular resistance, the level of cardiac output decreases back towards baseline while the level of systemic vascular resistance

increases back to baseline.[29, 30] The changes in cardiac output and systemic vascular resistance back to baseline are labeled with question marks because the mechanisms that mediate these changes are unclear and could involve a variety of factors such as "autoregulation," shifts in intravascular fluid volumes, decreases in flow mediated vasodilation, etc. SVR, systemic vascular resistance; RVR, renal vascular resistance; CO, cardiac output; BP, blood pressure.

(b) "Vasodysfunction" pathway whereby mutations underlying Mendelian disorders of salt-dependent hypertension (Table 1) can enable non-extreme increases in dietary salt intake to initiate hypertension. Non-extreme increases in salt intake are defined as increases within the range of usual daily salt intake observed in modern societies. In this pathway, the genetic alterations enable increases in dietary salt intake to initiate hypertension by causing "vasodysfunction", i.e., an inability to normally vasodilate and normally decrease systemic vascular resistance in response to the increased salt intake. This is depicted in the figure as an inhibitory effect of the mutations on the arterial vasodilation response that is normally expected to occur with an increase in salt intake. Note that the mutation-dependent inability to normally decrease systemic vascular resistance (SVR) in response to salt includes an inability to normally decrease renal vascular resistance (RVR) in response to salt. During initiation of salt-induced hypertension, RVR may actually increase in salt-sensitive subjects.

In this pathway, a mutation-dependent inhibitory effect on salt output is labeled with question marks. This is because mutation-dependent inhibitory effects on urinary

excretion of salt are not necessary for increases in salt intake to induce substantial increases in salt retention and transient increases in cardiac output. As shown in Figure 3a, increases in salt intake can induce substantial salt retention[29, 30, 35, 36, 37] and transient increases in cardiac output[29, 30] in normal people. Further, mutation-dependent inhibitory effects on urinary excretion of salt have not been established to be necessary for the mutations to enable increases in salt intake to initiate hypertension in these disorders. Thus, in this pathway, increases in salt retention, cardiac output and blood pressure induced by increasing salt intake may not necessarily depend on mutation-induced increases in activity of ENaC or NCC in the renal tubular epithelium. Moreover, even if mutation-induced alterations in renal tubular activity of ENaC or NCC do enhance the increases in salt retention and cardiac output normally induced by a high salt intake, the transient increases in cardiac output may often not be sufficient to initiate hypertension unless "vasodysfunction" is also present.

Note that with continuation of the high salt intake, salt balance (the state in which salt output matches salt intake) is eventually achieved and maintained. The salt-induced high blood pressure can promote salt output (natriuresis) and contribute to achievement of salt balance but it does not result in a level of "pressure-natriuresis" great enough to cause salt output to exceed salt intake and prevent high blood pressure from being sustained. This is because the extent of such "pressure-natriuresis" in salt-sensitive individuals is constrained by the abnormal renal vascular resistance response to increased intake of salt.

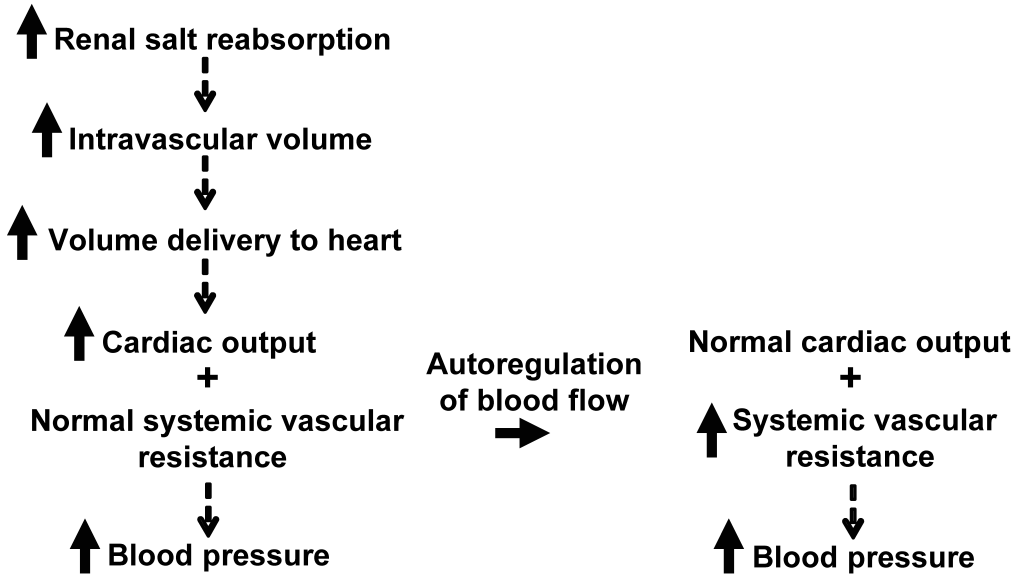
Note that while this pathway is focused on the initiation of salt-induced hypertension, it also depicts the decrease in cardiac output back toward baseline and the increase in vascular resistance above baseline that are believed to occur after the hypertension has been initiated. These changes that occur in cardiac output and systemic vascular resistance after the blood pressure has increased are labeled with question marks because the mechanisms that mediate these changes are unclear and could involve a variety of factors, not just "autoregulation." The pathway shown here leaves open the possibility that the mutations in these disorders might contribute to the abnormal increase in vascular resistance that occurs after the blood pressure has initially increased and that sustains the salt-dependent hypertension.

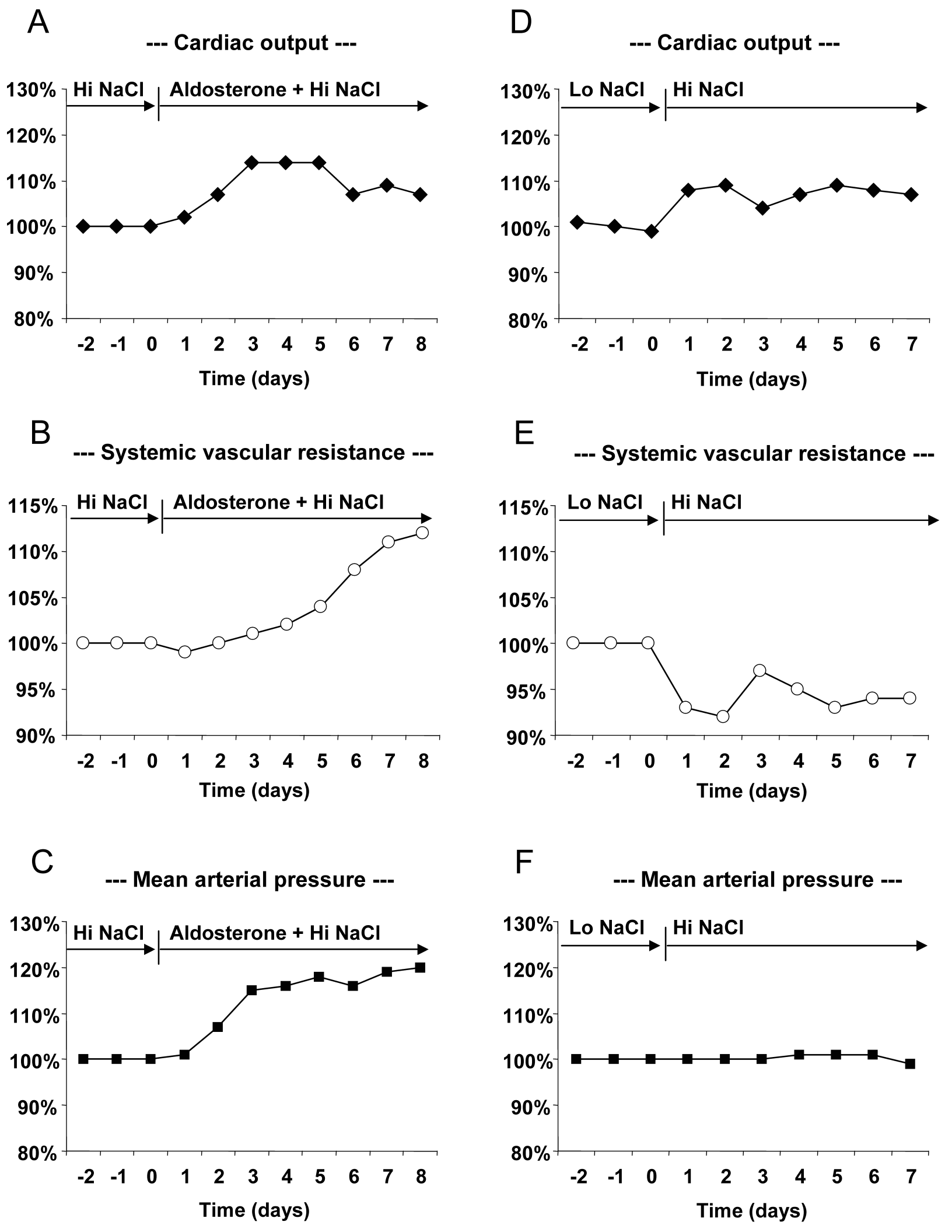
Table 1. Mendelian forms of salt-dependent hypertension

Clinical disorder	↑ Serum mineralocorticoids ?
Congenital adrenal hyperplasia	Yes
Glucocorticoid remediable aldosteronism	Yes
Familial hyperaldosteronism not remediable by glucocorticoids	Yes
Liddle syndrome	No
Hypertension exacerbated by pregnancy	No
Syndrome of apparent mineralocorticoid excess	No
Familial hyperkalemic hypertension	No

Causal mutations have been identified in all of these disorders.[1-4]

The Prevailing, "Volume-Loading" Theory of the Pathogenesis of NaCl-Dependent Hypertension




A
--- Cardiac output ---
Hi NaCl
Aldosterone + Hi NaCl
130%
120%
110%
100%
90%
80%
-2 -1 0 1 2 3 4 5 6 7 8
Time (days)
D
--- Cardiac output ---
Lo NaCl
Hi NaCl
130%
120%
110%
100%
90%
80%
-2 -1 0 1 2 3 4 5 6 7
Time (days)
B
--- Systemic vascular resistance ---
Hi NaCl
Aldosterone + Hi NaCl
115%
110%
105%
100%
95%
90%
-2 -1 0 1 2 3 4 5 6 7 8
Time (days)
E
--- Systemic vascular resistance ---
Lo NaCl
Hi NaCl
115%
110%
105%
100%
95%
90%
-2 -1 0 1 2 3 4 5 6 7
Time (days)
C
--- Mean arterial pressure ---
Hi NaCl
Aldosterone + Hi NaCl
130%
120%
110%
100%
90%
80%
-2 -1 0 1 2 3 4 5 6 7 8
Time (days)
F
--- Mean arterial pressure ---
Lo NaCl
Hi NaCl
130%
120%
110%
100%
90%
80%
-2 -1 0 1 2 3 4 5 6 7
Time (days)

Vasodysfunction Theory for Initiation of Mendelian Forms of NaCl-dependent Hypertension